#12

Commissioner of Patents and Trademarks
Box Patent Ext.
Washington, D.C. 20231

Dear Sir:

Pursuant to the provisions of 35 U.S.C. 156, Mead Johnson & Company, (hereinafter "Mead Johnson"), as a wholly-owned subsidiary of Bristol-Myers Company, hereby requests a two year extension of the term of U.S. Patent 4,182,763, i.e., an extension of the patent expiration date from January 8, 1997 to January 8, 1999. Mead Johnson is the assignee of U.S. Patent 4,182,763 from the inventors, all of whom were employees of Mead Johnson at the time of the invention. Agreements between Mead Johnson and the inventors vested all patent rights with Mead Johnson, as a result of which Mead Johnson is the owner of record and entitled to all rights of patent ownership including the right to apply for extension of the patent. U.S. Patent 4,182,763 covers the use of 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride known generically as buspirone hydrochloride. Buspirone hydrochloride is the "approved product" and is marketed by Mead Johnson under the brand name BUSPAR. Mead Johnson's parent, Bristol-Myers Company, is the holder of approved New Drug Application 18-731 (hereinafter called the "NDA") for BUSPAR. The NDA was approved by the FDA on September 29, 1986, in accordance with 21 U.S.C. 355(c), and permits the commercial marketing and use of BUSPAR in the management of anxiety disorders and the short term relief of the symptoms of anxiety. The FDA's approval of NDA 18-731 constituted the first permitted commercial marketing or use of product buspirone hydrochloride under 21 U.S.C. 355(c)(1).

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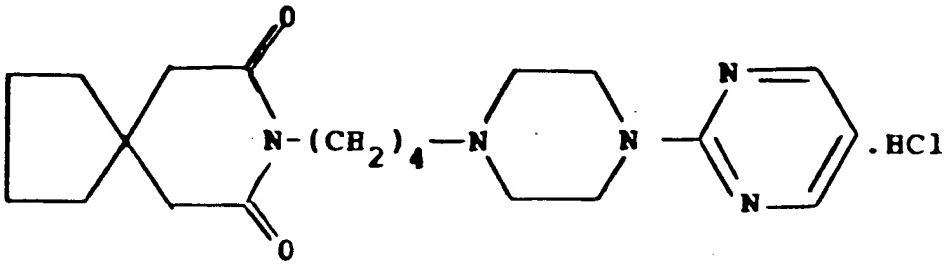
Section 1

Complete identification of the approved product

The approved product BUSPAR (generic name "buspirone hydrochloride") has:

a) the structural formula,



b) the empirical formula, $C_{21}H_{31}N_5O_2.HCl$

c) molecular weight of 422.0

d) the chemical name, 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro [4.5]decane -7,9-dione hydrochloride.

Section 2

Complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

Pursuant to Section 505(c)(1)(A) of the Federal Food, Drug and Cosmetic Act, (21 USC 355(c)(1)(A)), NDA 18-731 was approved and BUSPAR received permission for commercial marketing on September 29, 1986. While IND 8705 became effective on April 16, 1972, the applicable review period for the use claimed relative to BUSPAR as an antianxiety agent in U.S. Patent 4,182,763 began on October 22, 1976.

Prior to October 22, 1976, buspirone hydrochloride was studied for a different use than that claimed in the patent referred to above. A chronology of the regulatory review period is provided in Sections 9 and 10.

Section 3

Identification of the date on which the product received permission for commercial marketing.

The BUSPAR NDA (#18-731) was approved on September 29, 1986 pursuant to Section 505(c) of the Federal Food, Drug and Cosmetic Act. Buspirone hydrochloride is the only active ingredient of the approved product and has not been previously approved for commercial marketing or use.

Section 4

This application is being submitted within the sixty-day period provided by 35 U.S.C. 156(d)(1) since approval was granted on September 29, 1986 and the sixty-day period will lapse on November 28, 1986.

Section 5, 6

Complete identification of the patent. Copy of the patent.

The patent for which an extension is sought is U.S. Patent 4,182,763. It issued on January 8, 1980, on the application filed by George P. Casten, Gordon R. McKinney, Roger E. Newton, E. Crosby Tompkins, and John H. Weikel, Jr., on May 22, 1978. A copy of U.S. Patent 4,182,763, which is for BUSPIRONE ANTI-ANXIETY METHOD is provided as Attachment 1. U.S. Patent 4,182,763 names Mead Johnson as the Assignee.

Section 7

Copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

A copy of a certificate for correction of inventorship issued by the United States Patent and Trademark Office on March 18, 1986 is provided as Attachment 2. This certificate was requested to correct the inventorship of the patent by adding John E. Gajewski as one of the inventors.

A copy of a certificate of correction of Office mistake issued by the United States Patent and Trademark Office on July 8, 1986 is provided as Attachment 3. This certificate was requested to correct a mistake appearing in claim 5 and believed to have occurred during the printing of the patent.

(Section 8 begins on the next page)

Section 8

Statement that the patent claims a method of using the approved product

U.S. Patent 4,182,763 claims a method of using the approved product:

Claim 1 of U.S. Patent 4,182,763 covers a method of using the approved product BUSPAR in the palliative treatment of neurosis in which anxiety symptoms are prominent;

Claim 2 covers the use of BUSPAR by the oral route according to the method of claim 1;

Claim 3 covers the use of BUSPAR in patients suffering from anxiety neurosis according to the method of claim 2;

Claim 4 covers the use of BUSPAR in patients suffering from anxiety neurosis with depressive symptoms according to the method of claim 2;

Claim 5 (as corrected) covers an adult daily dose from 10 mg. to 60 mg. according to the method of claims 2, 3, or 4;

Claim 6 covers a daily divided dose administered b.i.d. according to the method of claim 5;

Claim 7 covers a daily divided dose administered t.i.d. according to the method of claim 5;

Claim 8 covers a maximum total dose of up to about 100 mg. according to the method of claim 2;

Claim 9 covers an adult therapeutic daily dose of from 20 mg. to 30 mg. according to the method of claims 2, 3, or 4.

(Section 9 begins on the next page)

Section 9

Relevant dates and information pursuant to 35 U.S.C. 156(g) to enable a determination of the applicable regulatory review period:

October 22, 1976	Effective date of IND Application No. 8705 for use as an antianxiety agent.*
December 15, 1982	Submittal date of NDA No. 18-731
September 29, 1986	NDA approval date

* IND Application No. 8705 became effective on April 16, 1972. However, the applicable review period for the use claimed relative to BUSPAR as an antianxiety agent (U.S. Patent No. 4,182,763) actually began on October 22, 1976.

(Section 10 begins on the next page)

Section 10

Brief description of the activities undertaken by the applicant during the applicable regulatory review period with respect to the approved product and significant dates applicable to such activities.

Bristol-Myers Company, on behalf of Mead Johnson & Company, undertook the development of this product to establish, by adequate and well-controlled clinical trials, its safety and effectiveness in the treatment of anxiety disorders and the short-term relief of symptoms of anxiety. Since this product was a new drug as defined under Section 201(p) of the Food, Drug and Cosmetic Act, an approved NDA for the product was required to be obtained under section 505(b) of the Food, Drug and Cosmetic Act prior to its commercial marketing.

An exemption under subsection(1) of Section 505 of the Food, Drug and Cosmetic Act was submitted to the FDA on October 22, 1976, requesting permission to evaluate BUSPAR in patients with anxiety symptoms. No request was made by the FDA that the sponsor continue to withhold or to restrict use of the drug in human subjects. The following is a chronology of activity that ensued:

October 22, 1976	Start-up of Clinical Study #657. This is the first clinical study protocol to evaluate BUSPAR in the treatment of anxiety submitted to FDA.
November 9, 1976	Phase II clinical testing initiated.

December 21, 1976	Start-up of Clinical Study #684. Clinical study protocol for this sleep study submitted to FDA.
March 15, 1977	Study report on metabolic disposition of radio labeled buspirone in man submitted to FDA (Study #599).
June 1, 1977	Start-up of Clinical Study #764. Clinical study protocol for this clinical efficacy study submitted to FDA.
June 16, 1977	Results of 2 year rat tumorigenicity study submitted to FDA.
June 9, 1978	Results of 18-month mouse tumorigenicity study submitted to FDA.
June 21, 1978	End Phase II meeting with FDA.
August 6, 1978	Response provided to FDA concerning chemistry questions raised in FDA letter of July 10, 1978.
November 28, 1978	Start-up of Clinical Study #1003. Clinical study protocol for this functional impairment study submitted to FDA.

March 26, 1979	Start-up of Clinical Studies #994, 996 and 1000. Clinical study protocols for these clinical efficacy studies submitted to FDA.
April 2, 1979	Start-up of Clinical Study #995. Clinical study protocol for this clinical efficacy study submitted to FDA.
April 4, 1979	Start-up of Clinical Studies #1012 and 1029. Clinical study protocols for these clinical efficacy studies submitted to FDA.
April 19, 1979	Start-up of Clinical Study #1041. Clinical study protocol for this clinical efficacy study submitted to FDA.
May 21, 1979	Start-up of Clinical Study #1032. Clinical study protocol for this clinical efficacy study submitted to FDA.
July 6, 1979	Start-up of Clinical Study #1048. Clinical study protocol for this clinical efficacy study submitted to FDA.
July 25, 1979	Start-up of Clinical Study #1049. Clinical study protocol for this clinical efficacy study submitted to FDA.

JANUARY 8, 1980	PATENT 4,182,763 ISSUED.
March 18, 1980	Meeting with FDA regarding drug abuse/physical dependence/scheduling considerations.
June 27, 1980	Start-up of Clinical Study #1183. Clinical study protocol for this clinical efficacy study submitted to FDA.
September 2, 1980	Start-up of Clinical Study #1207. Clinical study protocol for this fuctional impairment study submitted to FDA.
September 24, 1980	Meeting with FDA Drug Abuse Staff.
October 30, 1980	Meeting with FDA regarding biopharmaceutics issues.
November 6, 1980	Start-up of Clinical Study #1261. Clinical study protocol for this bioavailability study submitted to FDA.
January 30, 1981	Start-up of Clinical Study #1290. Clinical study protocol for this functional impairment study submitted to FDA.
March 31, 1981	Meeting with FDA regarding drug scheduling.

May 5, 1981	Start-up of Clinical Study #1324. Clinical study protocol for this neuroendocrine study submitted to FDA.
July 30, 1981	Meeting with FDA regarding biopharmaceutics - assay methodology and data analysis.
August 28, 1981	Start-up of Clinical Study #1367. Clinical study protocol for this abuse potential study submitted to FDA.
November 10, 1981	Pre NDA submission meeting with FDA.
December 23, 1981	Start-up of Clinical Study #1380. Clinical study protocol for abuse potential study submitted to FDA.
March 30, 1982	Chemical - Manufacturing - Control and Preclinical Pharmacology and Toxicology sections of BUSPAR NDA submitted to FDA.
June 10, 1982	Provided FDA information requested by Reviewing Chemist.
September 27, 1982	Start-up of Clinical Study #1480. Clinical study protocol for this neuroendocrine study submitted to FDA.

DECEMBER 15, 1982	SUBMISSION OF BUSPAR NDA #18-731 TO FDA.
January 19, 1983	Letter to FDA regarding BUSPAR drug class classification.
February 4, 1983	Provided FDA additional chemistry and biopharmaceutics information.
March 10, 1983	Provided FDA information requested by Biopharmaceutics Reviewer.
March 21, 1983	Provided FDA information requested by Reviewing Chemist.
March 31, 1983	Letter to FDA regarding BUSPAR drug classification.
April 28, 1983	Submission to FDA consisting of copies of published papers, preclinical reports and an update on human safety aspects.
May 10, 1983	Letter requesting meeting with FDA regarding status of NDA review.
May 16, 1983	Provided FDA clinical final reports for Studies #439, #532, and #606.
May 16, 1983	Provided FDA information requested by Reviewing Chemist.
June 13, 1983	Provided FDA updated pharmacologic summary and additional animal toxicology information.

August 6, 1983	Provided FDA additional statistical information to Reviewing Statistician for clinical studies #994 and #995.
August 22, 1983	Provided FDA documents for FDA Psychopharmacologic Drugs Advisory Committee Meeting.
September 22, 1983	Recommendation for approval given by FDA Psychopharmacologic Drugs Advisory Committee.
September 29, 1983	Provided FDA clinical abuse potential final report for Study #1380.
October 3, 1983	Provided FDA requested biopharmaceutics information and two biopharmaceutics reports.
October 6, 1983	Recommendation for non-scheduled status given by FDA Drug Abuse Advisory Committee.
October 6, 1983	Provided FDA requested information to Reviewing Chemist.
October 26, 1983	Provided FDA requested biophamaceutics information.
November 11, 1983	Provided FDA published papers, final printed container labels, preclinical data, and updated human safety information.
November 21, 1983	Provided FDA requested information on animal toxicology studies.

December 2, 1983	Information on an alternative tablet shape was provided to FDA.
December 2, 1983	Final biopharmaceutics report for Study #1490 was provided to FDA.
December 16, 1983	Letter for FDA records confirming incorporation into the NDA of our submission of August 6, 1983 in which additional statistical information was provided directly to the Reviewing Statistician for clinical Studies #994 and #995.
January 18, 1984	Letter from Ganes Chemicals, Inc. regarding Drug Master File.
January 19, 1984	Provided FDA requested information on Drug Master File.
February 17, 1984	Letter to FDA provided suggested dates for meeting with Biopharmaceutics Staff.
February 27, 1984	FDA letter requesting additional information on biopharmaceutics questions.
March 21, 1984	Provided FDA additional biopharmaceutics data.
March 28, 1984	Meeting with FDA staff regarding biopharmaceutics issues.

April 11, 1984	Provided FDA outline for a proposed animal study to Reviewing Pharmacologist.
July 5, 1984	Provided FDA requested information on plasma levels of a BUSPAR metabolite.
July 5, 1984	Response to FDA letter of February 27, 1984 regarding biopharmaceutics issues.
July 5, 1984	Provided FDA additional information on possible neuroendocrine effects of BUSPAR.
July 19, 1984	Information on an alternative BUSPAR tablet shape was provided to FDA.
August 9, 1984	Provided FDA an abstract of a paper on animal pharmacology of BUSPAR.
September 6, 1984	Revised draft of the proposed labeling for BUSPAR was provided to FDA.
September 27, 1984	FDA was provided with a safety update based on ongoing BUSPAR clinical studies and a revised draft of the proposed package insert.
December 21, 1984	Letter to Reviewing Chemist regarding alternative tablet shape.
January 11, 1985	Additional packaging specifications for BUSPAR were provided to FDA.

May 9, 1985	Meeting with FDA regarding status of ongoing NDA review.
July 29, 1985	Submission to FDA of requested reanalysis of clinical data and additional efficacy and safety data.
August 19, 1985	Submission to FDA of additional clinical efficacy data (US and Canadian composites).
October 10, 1985	Submission to FDA of data listings for clinical studies #1610, #1802, and #2044.
November 13, 1985	Submission to FDA of Bristol-Myers Company's onsite compliance audit for Study #2044.
December 2, 1985	Submission to FDA of proposed outline for safety update amendment.
December 3, 1985	FDA was advised that registration approval had been obtained for BUSPAR in Australia.
December 4, 1985	Letter for FDA records confirming the December 2, 1985 submission.
December 9, 1985	Additional case report forms submitted to FDA for clinical Study #1802.
December 16, 1985	Revised report submitted to FDA for clinical study #2044.

January 20, 1986	Comprehensive safety update for BUSPAR submitted to FDA as an amendment.
February 3, 1986	Addendum to safety update submitted to FDA.
February 6, 1986	Letter received from FDA stating that the safety update was considered a major amendment by regulation, that an additional 90 days was established for its review, and that the new due date is April 23, 1986.
February 26, 1986	Provided FDA requested additional information for clinical study #1012.
March 3, 1986	Letter addressed to FDA Medical Reviewer containing data on patient discontinuations for safety update.
March 11, 1986	Letter addressed to FDA Medical Reviewer enclosing draft statement concerning overall adverse event rate for inclusion in labeling.
March 13, 1986	Meeting date requested to discuss labeling.
March 17, 1986	Provided FDA requested information regarding clinical study #246 and copy of final study report for study #246.
March 17, 1986	FDA records disclose a duplicate 3/17/86 submission in their files.

March 26, 1986	Letter to Medical Officer which provides a copy of March 17, 1986 cover letter regarding clinical study #246.
March 26, 1986	Letter to FDA provided information on the status of BUSPAR patents.
April 1, 1986	Additional information provided to FDA on BUSPAR patents.
April 1, 1986	Letter addressed to FDA requesting a copy of the draft labeling proposed for BUSPAR.
June 17, 1986	Provided requested additional statistical analyses for clinical studies #994, #1802, and #2044.
June 19, 1986	Provided FDA requested additional clinical information on prior benzodiazepine use in patients for study #994, #1802, and #2044.
June 25, 1986	Provided to the Reviewing Statistician requested information regarding clinical study #1012.
July 9, 1986	Letter to FDA listing the 13 countries in which the registration of BUSPAR was approved.
July 17, 1986	Date of FDA letter stating that NDA application was approvable.

July 22, 1986	Letter informing the FDA that Bristol-Myers Comapny will file an amendment to the pending BUSPAR NDA.
August 5, 1986	Response to FDA letter of July 17, 1986 and a request for a meeting with FDA staff, if necessary, to resolve labeling issues.
August 19, 1986	Submission to FDA of several key publications and internal reports to support applicant's position that BUSPAR affects neurotransmitter systems other than the dopaminergic system.
August 20, 1986	Submission to FDA of: (a) summary information for six clinical studies dealing with effects of BUSPAR on depressive patients symptomatology; (b) two papers describing the effects of BUSPAR on patients with Parkinson's disease; and (c) a report describing the use of BUSPAR on a long term basis.
August 22, 1986	Submission to FDA of final safety update.

August 29, 1986	Meeting between FDA and Bristol-Myers Company representatives pertaining to labeling for BUSPAR. On occasion of that meeting, handed to FDA representatives two corrected pages to the safety update previously provided to FDA on August 22, 1986 and memorandum dated August 28, 1986 relating to the two corrected pages.
September 3, 1986	Letter to FDA dated September 2, 1986 provided final printed labeling and commitment to conduct the Phase IV studies requested by the FDA.
September 3, 1986	Additional information provided to FDA on dissolution specification for BUSPAR tablets.
September 4, 1986	Submission to FDA of a report on the safety and efficacy of BUSPAR in the elderly.
September 5, 1986	Provided FDA requested information on modal total daily dose of BUSPAR in the elderly.
September 29, 1986	FDA approval letter for NDA #18-731 received, granting permission for commercial marketing pursuant to Section 505(c)(1)(A) of the Federal Food, Drug and Cosmetic Act.

During the entire period from October 22, 1976 through December 14, 1982, the data generated on this product were under preparation for submission to FDA in support of the NDA. The NDA review period lasted from December 15, 1982 through September 29, 1986, with due diligence on the part of the sponsor during the entire regulatory review period.

(Section 11 begins on the next page)

Section 11

Patent eligibility and the length of extension claimed.

U.S. Patent 4,182,763 is eligible for extension for 2 years since:

(a) It claims use of the approved human drug product, BUSPAR;

(b) The term of said patent has never been previously extended;

(c) The application is submitted by the owner of the patent, Mead Johnson & Company;

(d) The product, BUSPAR, has been subject to regulatory review prior to commercial marketing or use;

(e) The product received permission for commercial marketing or use on September 29, 1986 and the application has been submitted within 60 days from that date;

(f) The term of the patent has not expired prior to this date of application; and

(g) No other patent term has been extended for the same regulatory review period for this product.

The length of extension claimed is the lesser of 2 years or the following calculated period of time:

Testing period began:	October 22, 1976
Patent issued:	January 8, 1980
NDA submitted:	December 15, 1982
NDA approved:	September 29, 1986

The testing period would equal the time between October 22, 1976 and December 15, 1982, less the period of time prior to the patent issuance (January 8, 1980), or 1,072 days.

The approval period would equal the time between December 15, 1982 and September 29, 1986 or 1,382 days.

The total extension would equal 1/2 X 1,072 + 1,382 or 1,918 days. Since this is greater than 2 years, the extension sought is for a 2 year period.

Section 12

Duty of Disclosure

The applicant hereby acknowledges his duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to this application for patent extension.

Section 13

The prescribed fee ($750.00) for receiving and acting upon the application for extension is attached. Inquiries and correspondence should be addressed to:

Isaac Jarkovsky, Esq.
Assistant General Counsel-Patents
Bristol-Myers Company
345 Park Avenue
New York, New York 10154
Telephone: 212-546-3653

Declaration

The undersigned, Vice President and Counsel of Mead Johnson & Company, applicant for extension of U.S. Patent 4,182,763, hereby avers that he is an authorized official of Mead Johnson & Company and:

1. Has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. 156;

2. Believes U.S. Patent 4,182,763 is subject to extension pursuant to A of the Guidelines for Extension of Patent Term issued by the U.S. Patent and Trademark Office on September 25, 1984 (Guidelines), and 35 U.S.C. 156;

3. Believes an extension for 2 years, the length claimed, is fully justified under 35 U.S.C. 156; and

4. Believes the patent for which the extension is being sought meets the conditions for extension of the term of the patent as set forth in B of the Guidelines.

Sincerely,

Robert N. Endries

Robert N. Endries
Vice President and Counsel
Mead Johnson & Company

United States Patent [19]

Casten et al.

[11] **4,182,763**

[45] **Jan. 8, 1980**

[54] **BUSPIRONE ANTI-ANXIETY METHOD**

[75] Inventors: **George P. Casten; Gordon R. McKinney; Roger E. Newton; E. Crosby Tompkins, all of Evansville; John H. Weikel, Jr., Mt. Vernon, all of Ind.**

[73] Assignee: **Mead Johnson & Company, Evansville, Ind.**

[21] Appl. No.: **908,597**

[22] Filed: **May 22, 1978**

[51] **Int. Cl.**[2] **A61K 31/505**

[52] **U.S. Cl.** **424/251**

[58] **Field of Search** **424/251**

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,717,634 2/1973 Wu et al. ..... 260/256.4 N

3,976,776 8/1976 Wu et al. 424/251

OTHER PUBLICATIONS

Wu et al., J. Med. Chem. 15, (1972), pp. 477–479.

Allen et al., Arzneim-Forsch, 24, No. 6, 917-992 (1974).

Sathancenthan et al., Current Therapeutic Research, 18, (5), 701–705 (1975).

Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—R. E. Carnahan; R. H. Uloth

[57] **ABSTRACT**

Buspirone hydrochloride is an effective anti-anxiety agent for the palliative treatment of neurotic patients in which symptoms of anxiety are predominant at doses which are without observable effect in either normal individuals or psychotic patients.

9 Claims, No Drawings

UNITED STATES PATENT AND TRADEMARK OFFICE

Certificate

Patent No. 4,182,763 Patented January 8, 1980

On petition requesting issuance of a certificate for correction of inventorship pursuant to 35 USC 256, it has been found that the above-identified patent, through error and without any deceptive intent, improperly sets forth the inventorship. Accordingly, it is hereby certified that the correct inventorship of this patent is George P. Casten, Gordon R. McKinney, Roger E. Newton, E. Crosby Tompkins, John H. Weikel, Jr. and John E. Gajewski.

Signed and Sealed this Eighteenth Day of March 1986.

Bradley R. Lewis

Office of the Deputy Assistant Commissioner for Patents.

Attachment 2

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,182,763

DATED : January 8, 1980

INVENTOR(S) : George P. Casten et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8, line 5, Claim 5, delete "2, 3 or 5" and insert -- 2, 3 or 4 --.

Signed and Sealed this

Eighth Day of July 1986

Attest: Priscilla A. Fuller

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks